

Stimulation on Demand: Closing the Loop on Deep Brain Stimulation

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High-frequency open-loop deep brain stimulation (DBS) has been used to alleviate Parkinson's symptoms for almost 20 years. In this issue of *Neuron*, Rosin et al. present a closed-loop real-time approach that improves DBS and shines light on the etiology of motor symptoms in Parkinson's disease.

In Parkinson's disease (PD), depletion of dopamine after degeneration of dopaminergic neurons (Carlsson, 1972; Hornykiewicz, 1966), mostly in substantia nigra pars compacta, leads to a variety of motor symptoms including bradykinesia, tremor, and rigidity. This dopamine depletion has consequences for the activity of cortico-basal ganglia circuits. A well-accepted view postulates that lack of dopamine in PD leads to increased activity of indirect pathway neurons (striatopallidal, which mainly express D2-type dopamine receptors) and decreased activity of direct pathway neurons (striatonigral, which mostly express D1-type dopamine receptors) (Albin et al., 1989), ultimately leading to increased activity in globus pallidus internus (GPi) and to overinhibition of thalamus and cortex. Another view proposes that dopamine depletion leads to abnormal network oscillations in basal ganglia, which produce excessive synchrony (Brown, 2003; Goldberg et al., 2004).

Currently, the first approach to alleviate PD symptoms is the administration of drugs to restore dopamine, most notably L-Dopa. However, L-Dopa typically becomes less effective with time. Another successful approach is the use of high frequency deep brain stimulation (DBS) in basal ganglia nuclei, mainly in the subthalamic nucleus (STN), the GPi, or the thalamus (Wichmann and Delong, 2006). The first reports of the use of DBS to treat -PD patients date to 1994 (Limousin et al., 1995). The paradigms currently used for DBS are based on continuous stimulation, or "open-loop DBS," because the stimulation pattern and intensity are set by an external stimulator and adjusted manually. Although the mechanisms by

which DBS stimulation works are still under debate, this strategy has helped more than 55,000 people suffering not only from PD but also from other motor disorders (Miller, 2009).

In this issue of *Neuron*, Rosin, Bergman, and colleagues (Rosin et al., 2011) develop a new strategy for DBS in the basal ganglia using a closed-loop paradigm, in which the activity of neurons in a reference brain area is used as the trigger for stimulating the target area (Figure 1). Using primates treated with MPTP, which causes dopaminergic neuron degeneration and PD-like symptoms (Burns et al., 1983), the authors compare the effects of different closed-loop paradigms and standard continuous or open-loop DBS protocols in akinesia and pallidal firing properties. These comparisons show that closed-loop paradigms with real-time adaptive stimulation have less undesirable side effects and more clinical benefits than standard paradigms.

One of the great advantages of closed-loop strategies relatively to standard DBS protocols is the possibility for automatic and constant adaptation to the dynamics of the disease in each patient over time. Currently, PD patients that undergo DBS treatments need to have periodic medical assistance by a trained clinician in order to have the stimulation parameters adjusted to the development of the disease, and parameters remain unchanged between adjustments. In this novel closed-loop DBS paradigm, neuronal spikes recorded in the primary motor cortex (M1) were used as an online trigger for stimulation (trains or single spikes) delivered to the GPi. This paradigm yielded a marked reduction in akinesia in all four limbs, but most notably

in the contralateral arm to the stimulation site, as measured by accelerometers. Importantly, this adaptive closed-loop DBS successfully triggered a reduction of pallidal firing rate and a decrease of oscillatory activity in GPi (Rosin et al., 2011).

The use of closed-loop DBS with motor cortex as the reference structure for triggering pallidal stimulation led to a reduction of stimulation frequency and also to an increase in the variability of the interstimulus interval when compared with standard high frequency stimulation. Could the improvements observed simply reflect the fact that the stimulation pattern was of lower frequency and more irregular? In order to demonstrate that the observed effects were due to the adaptive closed-loop nature of the stimulation, the authors performed two experiments. In one they applied an open-loop stimulation at low frequency (10 Hz versus standard DBS at 130 Hz). In another, they applied a stimulation pattern based on previous recordings from M1, with the same variability as the online adaptive stimulation pattern, but unrelated to the ongoing activity at the moment of the stimulation. In both cases no relevant improvements in behavior or neuronal modulation were observed, strengthening the conclusion that it was not the statistics of the stimulation pattern that promoted the behavioral improvements in closed-loop DBS, but rather the fact that the stimulation pattern reflected ongoing activity.

This study offers important insights into how DBS works. Previous studies suggested that there is increased neural activity in the STN of MPTP-treated primates (Crossman et al., 1985). Accordingly, lesioning the STN in the MPTP primate

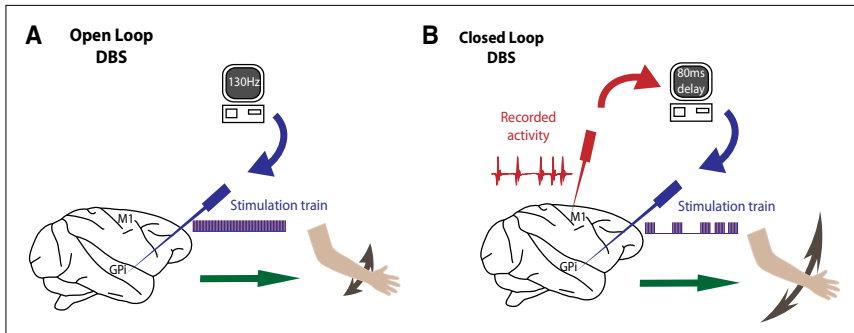


Figure 1. Illustration of an Open-Loop and an Adaptive Closed-Loop Deep Brain Stimulation (DBS) Paradigm

(A) Standard “open-loop” high-frequency (130 Hz) DBS consists of continuous stimulation of a target structure (i.e., internal segment of the globus pallidum, GPI) through an implanted electrode. (B) Adaptive “closed-loop” DBS consists of using the online activity of a reference structure (i.e., primary motor cortex, M1) as a trigger for stimulation of the target structure (i.e., GPI) after a certain delay (i.e., 80 ms). This results in a lower frequency and more irregular pattern of stimulation and promotes a substantial reduction of Parkinsonian akinesia compared with standard “open-loop” DBS protocols, by adapting the stimulation to the dynamics of cortico-basal ganglia networks.

model reverted the Parkinson-like symptoms (Bergman et al., 1990). Since both electrical stimulation of STN and STN lesions produced amelioration of PD symptoms, it was hypothesized that DBS leads to decreased activity in STN or decreased transmission from STN to GPI, therefore leading to reduced activity in GPI. Another suggestion has been that both STN lesions and DBS would disrupt the pathological oscillations observed in PD, leading to an improvement in motor symptoms; this view is supported by recent studies which suggest that DBS does not work by inhibiting STN neurons (Bar-Gad et al., 2004; Carlson et al., 2010; Gradinaru et al., 2009). Interestingly, Rosin and colleagues uncovered that the application of a closed-loop protocol in which GPI activity triggered GPI stimulation resulted in a reduction in pallidal discharge rate with no change in GPI oscillatory activity, and even in an increase in oscillatory activity in motor cortex (Rosin et al., 2011). In this situation, not only did akinesia in MPTP-treated primates not improve, but it got worse, suggesting that the ameliorating effects of DBS do not stem from reducing GPI activity, but likely from disrupting pathological oscillatory activity in the basal ganglia.

These experiments also give invaluable insight into the mechanisms underlying

the motor symptoms in PD. The fact that a decrease in GPI discharge rates with an increase in cortical oscillations resulted in an aggravation of akinesia, suggests that motor symptoms in PD are related to changes in oscillatory activity in cortico-basal ganglia circuits and not simply caused by an increase in the firing rate of GPI as a result of an imbalance between the activity of the direct and indirect pathways.

Although this study is very promising, it opens several questions for future experiments. Which are the optimal parameters for closed-loop DBS? Can different structures be used as reference or targets? What kind of signals can be used as triggers in order to allow for long-term stability? In this paradigm a single spike in the reference structure would trigger stimulation, but it may be difficult to record M1 spikes during long periods of time. The use of signals that could be recorded reliably for longer periods of time, like local field potential oscillations, could aid the long-term implementation of these close-loop strategies. It also remains to be determined how robust and stable the ameliorating effects would be after long-term exposure to such a treatment.

Furthermore, the approach taken by the authors can be the starting point to apply closed-loop DBS strategies to other

disorders, like neuropsychiatric disorders. It is becoming increasingly apparent that several diseases like schizophrenia, epilepsy, obsessive-compulsive disorders, Tourette syndrome, and depression could be treated using brain stimulation (Miller, 2009; Wichmann and Delong, 2006), and the real-time adaptive stimulation paradigm presented here could also offer significant advantages in the treatment of the associated symptoms. Hopefully, future studies in animal models will help disentangle not only how these pathologies emerge, but also define the best strategies to improve clinical outcomes.

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